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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,605	KOKEN ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 12-25 is/are pending in the application.

4a) Of the above claim(s) 22 and 23 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 12-21,24 and 25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement is made of applicants election without traverse of Group I.

2. Claims 12-25 are pending. Claims 22 and 23, drawn to non-elected inventions, are withdraw from consideration. Claims 12-21, 24 and 25 are examined on the merits.

Claim Objections

3. Claim 20 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 18. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 12-21, 24 and 25are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 12-21, 24 and 25 recite "PML protein" and/or "PML stabilization". It is unclear if the "PML" protein includes only the PML protein per se, or if the "PML protein" includes fusion proteins, such as PML-RAR . for purpose of examination, all alternatives will be considered.

(B) Claims 12 and 13 recite "PML stabilization". the metes and bounds of PLM stabilization is unclear. It cannot be construed in applicant is claiming the alteration in location of the PML protein from the microspeckled to nuclear bodies, or if applicant is referring to the increase or decrease of PML turnover rate. For purpose of examination all alternatives will be considered.

(C) Claim 21 recites "a compound having the same biological properties of arsenic". Arsenic has many biological properties such as the inactivation of enzymes through binding of the sulfhydryl groups within said enzymes, the replacement of phosphate in phosphorylation-dephosphorylation biochemical reactions and the induction of chromosomal aberrations, sister chromatid exchanges, DNA protein cross links and protein assoicated DNA strand breaks in mammalian cells (Chen et al, Blood, 1996, Vol. 88, pp. 1052-1061).

(D) Claim 21 recites "a substance assoicated with the PML protein". It is unclear what is intended in the metes and bounds of "assoicated with". Assoicated with can mean a physical assoication, or can be a mechanistic assoication, such as a signalling pathway. for purpose of examination all alternatives will be considered.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 24 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Kaltoft et al (US 2002/0001841, priority to July 2, 1998, 60/091,684).

Claim 24 is drawn in part to a method of inducing the death of undesirable cells or stimulation of an immune response comprising administering to a patient a caspase inhibitor and/ or a caspase substrate.

Kaltoft et al disclose a method of treating diseases, such as those of neoplastic origin [0080], comprising administration of specific disease-assoicated T-cells to a patient in need thereof [0150]. Kaltoft et al teach that the caspase inhibitor, z-VAD may be given during the administration to prevent AICD of the infused lymphocytes [0150]. The instant claims are drawn to a method comprising the administration of a caspase inhibitor and do not exclude methods comprising other active agents, such as disease assoicated T-cells.

8. Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Gianni et al (Blood, June 1, 1998, vol. 91, pp. 4300-4310).

Claim 21 is drawn in part to a method of inducing the death of undesirable cell in vitro comprising bringing undesirable cells in contact with an arsenic compound and a substance being assoicated with the PML protein.

Gianni et al disclose a method of inducing apoptosis in arsenic resistant and arsenic sensitive NB4 cells comprising contacting said cells with arsenic trioxide and retinoic acid (page 4305, first column, under the heading "RA and arsenic synergize to induce differentiation and apoptosis"). Gianni et al disclose that retinoic acid induces the catabolism of PML-RARalpha fusion proteins, thus retinoic acid fulfills the specific embodiment of claim 21 drawn to "a substance being assoicated with the PML protein"

9. Claim 21 is rejected under 35 U.S.C. 102(a) as being anticipated by Bazarbachi et al (Blood, Jan 1, 1999, Vol. 93, pp. 278-28) as evidenced by Chelbi-Alix et al (Leukemia, 1995, Vol. 9, pp. 2027-2033).

The specific embodiments of claim 21 are recited above.

Bazarbachi et al disclose a method for inducing the death of HTLIV-1 infected T-cells both in vitro and ex vivo comprising contacting said cells with arsenic trioxide and interferon-

alpha (page 280, first column "Apoptosis Studies" and second column "Ex Vivo studies").

Chelbi-Alix et al disclose that interferons induce the expression of PML in both normal cells and acute promyelocytic leukemia cells. Thus the method of Bazarbachi et al inherently fulfills the specific embodiment of claim 21 drawn to an agent inducing the expression of the PML protein. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 12-14 and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bazarbachi et al (Blood, Jan 1, 1999, Vol. 93, pp. 278-28) as evidenced by Chelbi-Alix et al (Leukemia, 1995, Vol. 9, pp. 2027-2033) and as evidenced by Zhu et al (PNAS, 1997, Vol. 94, pp. 3978-3983).

Claim 12 is drawn to a method of inducing the death of undesirable cells or the stimulation of an immune response comprising the administration to a patient of a) a substance

which promotes the targeting of the PML protein toward the nuclear bodies and/or PML stabilization; and b) the PL protein and/or an agent which induces the overexpression of the PML protein. claim 13 embodies the method of claim 12 wherein the substance that promotes the targeting of the PML protein toward the nuclear bodies and/or PML stabilization is selected from the group consisting of an arsenic compound, a compound having the same biological properties of arsenic, caspase inhibitors and caspase substrates. claim 14 embodies the method of claim 13 wherein the arsenic compound is arsenic trioxide. Claim 16 embodies the method of claim 12 wherein the agent inducing the overexpression of the PML protein is an interferon. Claim 17 embodies the method of claim 16 wherein said interferon is alpha, beta or gamma interferon. claims 18 and 20 embody the method of claim 12 wherein the administration of a) and b) is simultaneous or sequential.

Claim 19 is drawn to a method of inducing the death of undesirable cells and/or stimulating an immune response comprising administering to a patient a) an arsenic compound, a compound having the same biological properties a arsenic, caspase inhibitor or a caspase substrate and b) a interferon.

Bazarbachi et al teach a method for inducing the death of HTLIV-1 infected T-cells both in vitro and ex vivo comprising contacting said cells with arsenic trioxide and interferon-alpha (page 280, first column "Apoptosis Studies" and second column "Ex Vivo studies"). Chelbi-Alix et al disclose that interferons induce the expression of PML in both normal cells and acute promyelocytic leukemia cells. Bazarbachi et al suggest but do not teach that said method can be used in a clinical study for the treatment of HTLV-1 assoicated ATL (page 282, second column, last paragraph). Zhu et al teach that arsenic trioxide targets PML and PML/RARalpha onto nuclear bodies (abstract, lines 20-22), thus inherently fulfilling the specific embodiment of a substance which promotes the targeting of the PML protein toward the nuclear bodies.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer arsenic trioxide and interferon, to patients having HTLV-1 assoicated ATL. One of skill in the art would be motivated to do so by the suggestion of Bazarbachi et al that the combination of IFN and arsenic be used in a phase II clinical study for the treatment of HTLV-1 assoicated ATL. Applicant cannot rely upon the foreign priority papers to overcome

this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

12. Claims 12-14, and 16-21are rejected under 35 U.S.C. 103(a) as being unpatentable over He et al (Anticancer Research, 1997, Vol. 17, No. 5C, page 3927, abstract #6) in view of Muller et al (EMBO, Jan 2, 1998, vol. 17, pp. 61-70) and Chelbi-Alix et al (NATO ASI Series H: Cell Biology (1996, Vol. 99 (Tumor Biology), pp. 17-27) and Chen et al (blood, vol. 88, pp. 1052-1061) and Albert et al (Nature, March 5, 1998, Vol. 392, pp. 86-89).

The specific embodiments of the claims are se forth above.

He et al teach the administration of retinoic acid, IFN, arsenic trioxide , melarsoprol, or combinations thereof in transgenic models of APL. He et al do not specifically teach the combination of IFN and arsenic trioxide, or IFN and melarsoprol.

Muller et al teach that the post-translational modification of PML with SUMO-1 modulates the intracellular location of PML. Muller et al teach that arsenic trioxide increases the amount of PML-1-SUMO-1 conjugates that accumulate in the nuclear bodies. Muller et al teach that when ATL cells are exposed to arsenic trioxide PML-RARalpha is rapidly degraded but PML is not degraded (page 68, first column, lines 28-30). Muller et al teach that the kinetics of restoration of nuclear bodies is a direct consequence of PML-RARalpha destruction. Muller et al do not teach the molecular consequences of the administration of arsenic trioxide and interferon.

Chelbi-Alix et al teach that the PML/RARalpha fusion protein has been identified in acute promyleocytic leukemia, wherein the chimeric protein s a product of a t(15;17) translocation rendering RARalpha under control of the PML promoter. Chelbi-Alix et al teach that the PML/RARalpha fusion protein contains the functional domains of both PML and RARalpha and is the likely molecular basis of APL leukaemogenesis probably through alteration of PML and/or RARalpha functions (page 19, lines 1-13). Chelbi-Alix et al teach that in APL the PML/RARalpha fusion protein displaces the PML protein into microspeckeles rather than the normal location of nuclear bodies. Chelbi-Alix et al teach that the microspeckles are smaller and much more numerous than the speckled nuclear bodies (page 19, lines 15-25). Chelbi-Alix et al teach that IFNalpha treatment of NB4 cells increases the micropunctuate

pattern of PML and PML/RARalpha without altering their abnormal microspeckled location (without restoring the nuclear bodies) (page 21, lines 9-11). Chelbi-Alix et al teach that because IFNalpha increases PML/RARalpha in addition to PML, treatment with IFNalpha may enhance binding to RXR resulting in a further impairment of retinoic acid receptor function, which would act to increase the differentiation block toward nuclear receptors (page 21, line 12 to page 22, line 2). Chelbi-Alix et al teach that the demonstration that IFNalpha induces PML/RARalpha in APL cells is consistent with observations that the use of interferon in the treatment of APL can accelerate a patients leukemia (page 22, lines 7-10). Chelbi-Alix et al teach that overexpression of PML retards cell growth and PML sharply reduces the transforming effects of cooperating oncogenes and suppresses transformation by activated neu oncogene (page 23, line 4 to page 24, line 2). Chelbi-Alix et al conclude that IFN-induced PML protein has anti-oncogenic effects (page 24, lines 2-3).

It would have been prima facie obvious to one of skill in the art to combine arsenic trioxide with interferon for the treatment of leukemias assoicated with the fusion protein PML/RARalpha, or for the in vitro inhibition of said leukemia cells. One of skill in the art would be motivated to do so by the teachings of Muller et al on the selective degradation of the PML/RARalpha fusion protein after exposure of HTLV-1 assoicated ATL cells to arsenic trioxide; and the teachings of Chelbi-Alix on the anti-oncogenic effects of the PML protein and the induction of both the PML and PML/RARalpha proteins by exposure of APL cells to interferon alpha. One of skill in the art would have concluded that while the effects of arsenic trioxide on the selective degradation of the PML/RARalpha fusion protein are desirable, the addition of interferon would be t least additive in effect because it would be expected that the induction of PML would exert an anti-oncogenic effect and the concomitant induction of PML/RARalpha would be neutralized by arsenic trioxide degradation. Thus, one of skill in the art would expect that leukaemogenesis would be reversed by the decrease or elimination of PML/RARalpha and the increase in PML.

Claims 12-14, 16-20 are drawn in part to a method of stimulating an immune response. Chen et al teach that concomitant with the decrease in PML/RARalpha proteins, arsenic trioxide induces apoptosis in APL cells (abstract).

Alberts et al teach that dendritic cells acquire antigen from apoptotic cells and induce class-I restricted cryptozoic T-lymphocytes. Thus, it would be inherent in the method rendered obvious by the combination of He et la, Chelbi-Alix et al and Muller et al that the result of the combination of Interferon and arsenic trioxide would be apoptosis of APL cells, and that this apoptosis would inherently result in the presentation of antigen from the apoptotic APL cells and the consequent induction of antigen-specific CD+8 T cells which fulfills the specific limitation of stimulating an immune response.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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